1. INTRODUCTION

This document presents an integrated summary of available information related to exposure to and possible health effects of dioxin and related compounds. It also presents a short risk characterization, which is a concise statement of dioxin science and the public health implications of both general population exposures from environmental “background”[1]and incremental exposures associated with proximity to sources of dioxin and related compounds. Even though it summarizes key findings developed in the exposure and health assessment portions (Parts I and II, respectively) of the Agency’s dioxin reassessment, it is meant to be detailed enough to stand on its own for the average reader. Readers are encouraged to refer to the more detailed documents for further information on the topics covered here and to see complete literature citations. These documents are:

Estimating Exposure to Dioxin-like Compounds: This document, hereafter referred to as Part I, the Exposure Document, is divided into four volumes: (1) Executive Summary; (2) Sources of Dioxin in the United States; (3) Properties, Environmental Levels, and Background Exposures; and (4) Site-Specific Assessment Procedures.

Health Assessment Document for 2,3,7,8-TCDD and Related Compounds: This document, hereafter referred to as Part II, the Health Document, contains two volumes with nine chapters covering pharmacokinetics, mechanisms of action, epidemiology, animal cancer and various non-cancer effects, toxicity equivalence factors (TEFs), and dose-response.

Parts of this integrative summary and risk characterization go beyond individual chapter findings to reach general conclusions about the potential impacts of dioxin-like compounds on human health. This document specifically identifies issues concerning the risks that may be occurring in the general population at or near population background exposure levels. It articulates the strengths and weaknesses of the available evidence for possible sources, exposures and health effects, and presents assumptions made and inferences used in reaching conclusions regarding these data. The final risk characterization provides a synopsis of dioxin science and its

---

[1]The term “background” exposure has been used throughout this reassessment to describe exposure of the general population, who are not exposed to readily identifiable point sources of dioxin-like compounds. Most (>95%) of this exposure results from minute amounts of dioxin-like compounds being present in dietary fat.

implications for characterizing hazard and risk for use by risk assessors and managers inside and outside EPA and by the general public.

This document (Part III) is organized as follows:

1. Introduction - This section describes the purpose/organization of, and the process for developing, the report; defines dioxin-like compounds in the context of the EPA re-assessment; and explains the Toxicity Equivalency (TEQ) concept.

2. Effects Summary - This section summarizes the key findings of the Health Document and provides links to relevant aspects of exposure, mechanisms, and dose-response.

3. Mechanisms and Mode of Dioxin Action - This section discusses the key findings on effects in terms of mode of action. It uses the "Mode-of-Action Framework" recently described by the WHO/IPCS Harmonization of Approaches to Risk Assessment Project and contained in the Agency's draft Guidelines for Carcinogen Risk Assessment as the basis for the discussions.

4. Exposure Summary - This section summarizes the key findings of the Exposure Document and links them to the effects, mechanisms, and dose-response characterization.

5. Dose Response Summary - This section summarizes approaches to dose response that are found in the Health Document and provides links to relevant aspects of exposure and effects.

6. Risk Characterization - This section presents conclusions based on an integration of the exposure, effects, mechanisms and dose response information. It also highlights key assumptions and uncertainties.

The process for developing this risk characterization and companion documents has been open and participatory. Each of the documents has been developed in collaboration with scientists from inside and outside the Federal Government. Each document has undergone extensive internal and external review, including review by EPA's Science Advisory Board (SAB). In September 1994, drafts of each document, including an earlier version of this risk characterization, were made available for public review and comment. This included a 150-day comment period and 11 public meetings around the country to receive oral and written comments. These comments, along with those of the SAB, have been considered in the drafting of this final document. The Dose-Response Chapter of the Health Effects Document underwent peer review in 1997; an earlier version of this Integrated Summary and Risk Characterization underwent development and review in 1997 and 1998, and comments have been incorporated. In addition, as requested by the SAB, a chapter on Toxicity Equivalence has been developed and will undergo review in parallel with this document. When complete, and following final SAB review, the comprehensive set of background documents and this integrative summary and risk characterization will be published as final reports and replace the previous dioxin assessments as the scientific basis for EPA decision-making.

1.1. DEFINITION OF DIOXIN-LIKE COMPOUNDS

As defined in Part I, this assessment addresses specific compounds in the following chemical classes: polychlorinated dibenzodioxins (PCDDs or CDDs), polychlorinated dibenzofurans (PCDFs or CDFs), polybrominated dibenzodioxins (PBDDs or BDDs), polybrominated dibenzofurans (PBDFs or BDFs), and polychlorinated biphenyls (PCBs), and describes this subset of chemicals as "dioxin-like." Dioxin-like refers to the fact that these compounds have similar chemical structure, similar physical-chemical properties, and invoke a common battery of toxic responses. Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. The CDDs include 75 individual compounds; CDFs include 135 different compounds. These individual compounds are referred to technically as congeners. Likewise, the BDDs include 75 different congeners and the BDFs include an additional 135 congeners. Only 7 of the 75 congeners of CDDs, or of BDDs, are thought to have dioxin-like toxicity; these are ones with chlorine/bromine substitutions in, at a minimum, the 2, 3, 7, and 8 positions. Only 10 of the 135 possible congeners of CDFs or of BDFs are thought to have dioxin-like toxicity; these also are ones with substitutions in the 2, 3, 7, and 8 positions. This suggests that 17 individual CDDs/CDFs, and an additional 17 BDDs/ BDFs, exhibit dioxin-like toxicity. The database on many of the brominated compounds regarding dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment.

There are 209 PCB congeners. Only 12 of the 209 congeners are thought to have dioxin-like toxicity; these are PCBs with 4 or more lateral chlorines with 1 or no substitution in the ortho position. These compounds are sometimes referred to as coplanar, meaning that they can assume a flat configuration with rings in the same plane. Similarly configured polybrominated biphenyls (PBBs) are likely to have similar properties. However, the database on these compounds with regard to dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment. Mixed chlorinated and brominated congeners of dioxins, furans, and biphenyls also exist, increasing the number of compounds potentially considered dioxin-like within the definitions of this assessment. The physical/chemical properties of each congener vary according to the degree and position of chlorine and/or bromine substitution. Very little is known about occurrence and toxicity of the mixed (chlorinated and brominated) dioxin, furan, and biphenyl congeners. Again, these compounds have not been explicitly considered in this assessment. Generally speaking, this assessment focuses on the 17 CDDs/CDFs and a few of the coplanar PCBs that are frequently encountered in source characterization or environmental samples. While recognizing that other “dioxin-like” compounds exist in the chemical classes discussed above (e.g., brominated or chlorinated/brominated congeners) or in other chemical classes (e.g., halogenated naphthalenes or benzenes, azo- or azoxybenzenes), the evaluation of less than two dozen chlorinated congeners is generally considered sufficient to characterize environmental “dioxin.”

The chlorinated dibenzodioxins and dibenzofurans are tricyclic aromatic compounds with similar physical and chemical properties. Certain of the PCBs (the so-called coplanar or mono-ortho coplanar congeners) are also structurally and conformationally similar. The most widely studied of this general class of compounds is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This compound, often called simply “dioxin,” represents the reference compound for this class of compounds. The structure of TCDD and several related compounds is shown in Figure 1-1. Although sometimes confusing, the term “dioxin” is often also used to refer to the complex mixtures of TCDD and related compounds emitted from sources, or found in the environment or in biological samples. It can also be used to refer to the total TCDD “equivalents” found in a sample. This concept of toxicity equivalence is discussed extensively in Part II, Chapter 9, and is summarized below.

1.2. TOXICITY EQUIVALENCE FACTORS

CDDs, CDFs, and PCBs are commonly found as complex mixtures when detected in environmental media and biological tissues, or when measured as environmental releases from specific sources. Humans are likely to be exposed to variable distributions of CDDs, CDFs, and dioxin-like PCB congeners that vary by source and pathway of exposures. This complicates the human health risk assessment that may be associated with exposures to variable mixtures of dioxin-like compounds. In order to address this problem, the concept of toxicity equivalence has been considered and discussed by the scientific community, and toxic equivalency factors (TEFs) have been developed and introduced to facilitate risk assessment of exposure to these chemical mixtures.

On the most basic level, TEFs compare the potential toxicity of each dioxin-like compound comprising the mixture to the well-studied and understood toxicity of TCDD, the most toxic member of the group. The background and historical perspective regarding this procedure is described in detail in Part II, Chapter 9, and in Agency documents (U.S. EPA 1987, 1989, 1991a). This procedure involves assigning individual TEFs to the 2,3,7,8 substituted CDD/CDF congeners and “dioxin-like” PCBs. To accomplish this, scientists have reviewed the toxicological databases along with considerations of chemical structure, persistence, and resistance to metabolism, and have agreed to ascribe specific, "order of magnitude" TEFs for each dioxin-like congener relative to TCDD, which is assigned a TEF of 1.0. The other congeners have TEF values ranging from 1.0 to 0.00001. Thus, these TEFs are the result of scientific judgment of a panel of experts using all of the available data and are selected to account for uncertainties in the available data and to avoid underestimating risk. In this sense, they can be described as "public health conservative" values. To apply this TEF concept, the TEF of each congener present in a mixture is multiplied by the respective mass concentration and the products are summed to represent the 2,3,7,8-TCDD Toxic Equivalence (TEQ) of the mixture, as determined by Equation 1-1.

$$TEQ \cong \sum_{i-n}\left(Congener_i \times TEF_i\right) + \left(Congener_j \times TEF_j\right) + \ldots\ldots\left(Congener_n \times TEF_n\right) \qquad (1\text{-}1)$$

The TEF values for PCDDs and PCDFs were originally adopted by international convention (U.S. EPA, 1989a). Subsequent to the development of the first international TEFs for CDD/Fs, these values were further reviewed and/or revised and TEFs were also developed for PCBs (Ahlborg et al., 1994; van den Berg et al, 1998). A problem arises in that past and present quantitative exposure and risk assessments may not have clearly identified which of three TEF schemes was used to estimate the TEQ. This reassessment introduces a new uniform TEQ nomenclature that clearly distinguishes between the different TEF schemes and identifies the congener groups included in specific TEQ calculations. The nomenclature uses the following abbreviations to designate which TEF scheme was used in the TEQ calculation:

1. I-TEQ refers to the International TEF scheme adopted by EPA in 1989 (U.S. EPA, 1989a). See Table 1-1.
2. TEQ-WHO_{94} refers to the 1994 World Health Organization (WHO) extension of the I-TEF scheme to include 13 dioxin-like PCBs (Ahlborg et al., 1994). See Table 1-2.
3. TEQ-WHO_{98} refers to the 1998 WHO update to the previously established TEFs for dioxins, furans, and dioxin-like PCBs (van den Berg et al., 1998). See Table 1-3.

The nomenclature also uses subscripts to indicate which family of compounds is included in any specific TEQ calculation. Under this convention, the subscript D is used to designate dioxins, the subscript F to designate furans and the subscript P to designate PCBs. As an example, "TEQ_{DF}-WHO_{98}" would be used to describe a mixture for which only dioxin and furan congeners were determined and where the TEQ was calculated using the WHO_{98} scheme. If PCBs had also been determined, the nomenclature would be "TEQ_{DFP}-WHO_{98}." Note that the designations TEQ_{DF}-WHO_{94} and I-TEQ_{DF} are interchangeable, as the TEFs for dioxins and furans are the same in each scheme. Note also that in the current draft of this document, I-TEQ sometimes appears without the D and F subscripts. This indicates that the TEQ calculation includes both dioxins and furans.

This reassessment recommends that the WHO_{98} TEF scheme be used to assign toxicity equivalence to complex environmental mixtures for assessment and regulatory purposes. Later sections of this document describe the mode(s) of action by which dioxin-like chemicals mediate biochemical and toxicological actions. These data provide the scientific basis for the TEF/TEQ methodology. In its 20-year history, the approach has evolved, and decision criteria supporting the scientific judgment and expert opinion used in assigning TEFs has become more transparent. Numerous states, countries, and several international organizations have evaluated and adopted this approach to evaluating complex mixtures of dioxin and related compounds (Part II, Chapter 9). It has become the accepted methodology, although the need for research to explore alternative approaches is widely endorsed. Clearly, basing risk on TCDD alone or assuming all chemicals are equally potent to TCDD is inappropriate on the basis of available data. Although uncertainties in the use of the TEF methodology have been identified and are described later in this document and in detail in Part II, Chapter 9, one must examine the use of this method in the broader context of the need to evaluate the potential public health impact of complex mixtures of persistent, bioaccumulative chemicals. It can be generally concluded that the use of TEF methodology for evaluating complex mixtures of dioxin-like compounds decreases the overall uncertainties in the risk assessment process as compared to alternative approaches. Use of the latest consensus values for TEFs assures that the most recent scientific information informs this "useful, interim approach" (U.S. EPA, 1989a; Kutz et al., 1990) to dealing with complex environmental mixtures of dioxin-like compounds. As stated by the U.S. EPA Science Advisory Board (U.S. EPA, 1995), "The use of the TEFs as a basis for developing an overall index of public health risk is clearly justifiable, but its practical application depends on the reliability of the TEFs and the availability of representative and reliable exposure data." EPA will continue to work with the international scientific community to update these TEF values to assure that the most up-to-date and reliable data are used in their derivation and to evaluate their use on a periodic basis. One of the limitations of the use of the TEF methodology in risk assessment of complex environmental mixtures is that the risk from non-dioxin-like chemicals is not evaluated in concert with that of dioxin-like chemicals. Future approaches to the assessment of environmental mixtures should focus on the development of methods that will allow risks to be predicted when multiple mechanisms are present from a variety of contaminants.

1.3. UNDERSTANDING EXPOSURE/DOSE RELATIONSHIPS FOR DIOXIN-LIKE COMPOUNDS

Dose can be expressed as a variety of metrics (e.g., daily intake, serum concentrations, steady-state body burdens, or area under the plasma concentration versus time curve [AUC]). Ideally, the best dose metric is that which is directly and clearly related to the toxicity of concern by a well-defined mechanism. In the mechanism-based cancer modeling for TCDD which will be discussed later, for instance, instantaneous values of a dose-metric, CYP1A2 or EGF receptor concentrations are used as surrogates for mutational rates and growth rates within a two-stage cancer model. The utility of a particular metric will also depend upon the intended application and the ability to accurately determine this dose metric. For example, if concentration of activated Ah receptors in a target tissue was determined to be the most appropriate dose metric for a particular response in laboratory animals, its utility would be questionable since we presently have no means to determine these values in humans.

In this reassessment of the health effects of dioxins, dose is used to understand the animal-to-human extrapolations, comparing human exposure as well as comparing the sensitivity of different toxic responses. Previous assessments of TCDD have used daily dose as the dose metric and applied either an allometric scaling factor or an uncertainty factor for species extrapolation. The present assessment uses steady-state body burdens as the dose metric of choice. One reason for the change in dose metrics is that recent data demonstrate that the use of either allometric scaling or uncertainty factors underestimates the species differences in the pharmacokinetic behavior of TCDD and related chemicals. This is due to persistence and accumulation of dioxins in biological systems and to the large (approximately 100-fold) difference in half-lives between humans and rodents.

When extrapolating across species, steady-state body burden appears to be the most appropriate dose metric. The choice of body burden as the dose metric is based on scientific and pragmatic approaches. As stated earlier, the best dose metric is that which is directly and clearly related to the toxicity of concern. For dioxins, there is evidence in experimental animals that tissue concentrations of dioxins is an appropriate dose metric for the developmental, immunological, and biochemical effects of dioxins (Hurst et al., 2000; Van Birgelen et al., 1996; Walker et al., 1998). Comparing target tissue concentrations of dioxins between animals and humans is impractical. In humans, the tissues for which we have estimates of the concentration are limited to those that may not be the target tissue of concern, such as serum, blood, or adipose tissue. However, tissue concentrations are directly related to body burdens of dioxins. Therefore, steady-state body burdens can be used as surrogates for tissue concentrations.

Body burdens have been estimated through two different methods. Serum, blood, or adipose tissue concentrations of dioxins are reported as pg/g lipid. Evidence supports the assumption that TCDD and related chemicals are approximately evenly distributed throughout the body lipid. Using the tissue lipid concentrations and the assumption that TCDD is equally distributed based on lipid content, body burdens are calculated by multiplying the tissue concentration by the percent body fat composition. One potential problem for estimating body burdens is the hepatic sequestration of dioxins. In rodents, dioxins accumulate in hepatic tissue to a greater extent than predicted by lipid content. This sequestration is due to CYP1A2, which binds dioxins. There is also evidence in humans that dioxins are sequestered in hepatic tissue. Estimating body burdens on serum, blood, or adipose tissue concentrations may underpredict true body burdens of these chemicals. This underprediction should be relatively small. As liver is approximately 5% of body weight, even a 10-fold sequestration in hepatic tissue compared to adipose tissue would result in a 50% difference in the body burden estimated using serum, blood, or adipose tissue concentrations. In addition, the sequestration is dose-dependent, and at human background exposures, hepatic sequestration should not be significant.

A second method for determining body burdens is based on estimates of the daily intake and half-life of dioxins. Limitations on estimating body burden through this method are dependent upon the accuracy of the estimates for intake and half-life. Historically, intakes of dioxins have varied and there is some uncertainty about past exposures. In addition, little is known about the half-life of dioxins at different life stages, although there is a relationship between fat composition and elimination of dioxins. Finally, depending on the exposure scenario, using the half-life of TCDD for the TEQ concentrations may result in some inaccuracies. While the chemicals that contribute most to the total TEQ, such as the pentachlorodioxins and dibenzofurans and PCB 126, have similar half-lives to TCDD, other contributors to the total TEQ have significantly different half-lives. This document uses pharmacokinetic modeling in a number of places where it is assumed that the 7-year half-life for TCDD can be applied to the TEQ_{DFP} of a mixture of dioxins, furans, and PCBs. The validity of this assumption was tested in the following way. First, congener-specific half-lives and intake rates were identified for each of the dioxin and furan congeners with nonzero TEFs. These half-lives and intakes were input into a one-compartment, steady-state pharmacokinetic model to get congener-specific tissue concentrations. The congener-specific tissue levels were summed to get an overall TEQ_{DF} tissue value. Second, the pharmacokinetic model was run using the 7-year half-life and total TEQ_{DF} intake to get a TEQ_{DF} tissue concentration. Both of these modeling approaches yielded very similar TEQ_{DF} tissue levels. Although this exercise did not include PCBs (because of lack of half-life estimates), and the congener-specific half-lives for many of the dioxins and furans have limited empirical support, it provides some assurance that this is a reasonable approach (see full discussion in Part I, Volume 3, Chapter 4).

Body burdens also have an advantage as a dose metric when comparing occupational or accidental exposures to background human exposures. In the epidemiological studies, the external exposure and the rate of this exposure are uncertain. The only accurate information we have is on serum, blood, or adipose tissue concentrations. Because of the long biological half-life of TCDD, these tissue concentrations of dioxins are better markers of past exposures than they are of present exposures. Hence, body burdens allow for estimations of exposure in these occupational and accidentally exposed cohorts. In addition, this dose metric allows us to compare these exposures with those of background human exposures.

The use of body burden, for many effects within species and, particularly, for cross-species scaling, appears to provide a better dose metric than daily dose. There is sufficient scientific evidence to support the use of body burden as a reasonable approximation of tissue concentrations. Future efforts to better understand the dose-response relationships for the effects of dioxin-like chemicals should provide insight into determining better dose metrics for this class of chemicals.